

1993

The Dynamics of Growth-Factor-Modified Immune-Response to Cancer Growth: One-Dimensional Models

J. A. Adam

Old Dominion University, jadam@odu.edu

Follow this and additional works at: https://digitalcommons.odu.edu/mathstat_fac_pubs

 Part of the [Applied Mathematics Commons](#), and the [Computer Sciences Commons](#)

Repository Citation

Adam, J. A., "The Dynamics of Growth-Factor-Modified Immune-Response to Cancer Growth: One-Dimensional Models" (1993). *Mathematics & Statistics Faculty Publications*. 96.
https://digitalcommons.odu.edu/mathstat_fac_pubs/96

Original Publication Citation

Adam, J. A. (1993). The dynamics of growth-factor-modified immune-response to cancer growth: One-dimensional models. *Mathematical and Computer Modelling*, 17(3), 83-106. doi:10.1016/0895-7177(93)90041-v

organism as a whole. When the B-cells encounter the antigen (foreign "invader"), they differentiate further into large cells that proliferate and secrete chemical substances capable of neutralizing the antigen (antibodies). On the other hand, the T-cells, after further differentiation in the thymus, regulate the action of the B-cells by both activation (or enhancement) and inhibition (or suppression). They are also involved in immune responses that are directly cell-mediated. This function—cytotoxic activity—is shared by other cellular species of the immune system, such as macrophages. There is a sequence of increasingly sophisticated mathematical models in the literature that concerns such cell-mediated responses. Early theoretical studies were carried out in [4] (see references therein) and extended in considerable detail, especially in [5,6]. These works did not address the spatio-temporal problem of antibody-antigen dynamics, but are nevertheless extremely important to an understanding of (to quote Bell) a "simplest possible" model of immune response. Lefever and Garay [7] also developed a model of local cellular interactions in tumors, and under some reasonable simplifying assumptions, obtained a local balance equation for the number x of target (cancer) cells. Lefever and Garay summarized much of the data on cytotoxic and rejection parameters for the various immune response cells. They also estimated the mean time for complete extinction of the neoplastic cell population. This is important, because once the malignant cell production rate is inhibited, and the T-cell cytotoxicity ensures tumor rejection, tumor recurrence is certainly possible as long as a single neoplastic cell exists.

The next development along these lines was provided by Prigogine and Lefever [8]. They included spatial (1-dimensional) variations in a set of local balance equations for the cancer cells (dead and alive) and effector cells. This formulation leads directly to the concept of reaction-diffusion equations, which have received considerable attention in the last decades (for an early account, see [9]). Most of their subsequent analysis in that paper pertains to the scalar case which arises when the effector cells diffuse much faster than the cancer cells "propagate" by cellular replication, and when the dead cells are eliminated rapidly. The governing equation is nevertheless extremely rich in its structure, and it is this richness of structure that we address here in terms of the modifying effects of growth factors.

A type of reaction-diffusion analysis related to [8] above has been carried out by Lefever and Erneux [10]. They incorporated nonlinear diffusion terms and used perturbation techniques to construct slowly-varying travelling wave solutions to a system of four coupled reaction-diffusion equations. They also examined the sensitivity of the system to environmental fluctuations, and the dependence of bistability on these fluctuations. Cellular environments depend, as we have noted above, on a plethora of factors (genetic, metabolic, geometric, hormonal, immunological, membranous, radiation, temperature, etc.) which can be expected to fluctuate somewhat over time (at best they may be constant on average). The authors showed that even in the presence of large, extremely rapid and completely incoherent (memoryless) noise (like Gaussian white noise), the stationary state of the tumor growth model remains remarkably coherent. Furthermore, by increasing the variance of the noise, it is possible to induce bistability in a system which displays none (for certain parameter ranges) under constant environmental conditions. Clearly, this modifies the mechanism of tumor growth—indeed, tumor rejection seems facilitated [11].

More recently, Qi [12] has re-examined some of the above models by Lefever and co-workers. He has reduced his system to one in two variables x and p , representing the density of living and dead cancerous cells, respectively. Obviously the dynamics of this system can be very complex as the parameter domains vary: we will be content in this paper to examine in detail the response of a spatio-temporal system with one dependent variable (x) to various growth terms which are chosen both for their suggestive behavior as growth factor modifications, and for their analytic simplicity. The analysis carried out here will form the basis for comparison with more sophisticated quantitative models incorporating growth factor effects and interactions as this information becomes available.

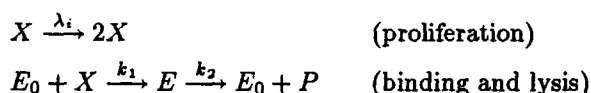
As we have noted, tumor growth is a function not only of the tumor cells themselves and their environment, but also upon their interactions with each other and normal cells. Most notably, there is much interest with regard to "Transforming Growth Factors" (TGF's, see [13]). Sporn and Todaro [14] and Sporn and Roberts [15] have proposed two pathways for the involvement of growth factors in cellular growth control. Thus, an *autocrine* control loop corresponds to a type of self-stimulation, whereby a cell secretes a hormone-like substance for which the cell itself

has surface receptors. Recently, this concept has been extended to include inhibitory control mechanisms also [16]. The other type of control loop is *paracrine*, in which local release of growth factors affects other types of cells in the surrounding microenvironment. The primary effect of paracrine factors is an increase of the organism's ability, at a local level, to support the tumor. Thus, the tumor manipulates its environment to its own advantage.

An important related aspect of the above discussion is that of cancer metastasis. Once a tumor cell enters the blood stream or lymphatic system, it runs a major risk, as we have noted, of being wiped out by an immune system on the lookout for such cells. Tumor cells may escape this danger, however, by losing the cell surface molecules (see [17]) that are needed for recognition by some immune cells. Tumor cells may also "protect themselves" against immune attack by forming aggregates. If these avoidance processes are successful, there is still no guarantee that all of the cells arriving at a potentially new organ site are capable of growing there, however. The response may well be related to the presence of growth factors produced by that cell's microenvironment. Metastatic cells may become responsive to the growth factor(s) by switching on the gene(s) encoding the receptor(s) for it (them). As pointed out in [17], any or all of the adaptations that tumor cells must undergo to become metastatic might provide points of attack for therapies aimed at preventing or treating disseminated cancer.

The purpose of this paper is to provide a blend of mathematical modeling and phenomenology: to represent in phenomenological terms the effects of different types of growth factors (characterized here as deviations from the normal logistic-type growth rates) on the spatio-temporal dynamics of a simple one-dimensional model incorporating the immune response to a cancer cell population. This affords direct comparison with some of the results from earlier models (particularly that of [8]), and provides a basis for more sophisticated modeling as more information on growth factors and their nature becomes available.

We consider a volume element containing a total number of N_i cells (the subscript i runs from 1 to 4 depending on which model of growth factor is used). N_i represents a saturation level for the cancer cells in that local volume element. The population of tumor cells is denoted by $X(\hat{r}, t)$, while the cytotoxic or "effector" cells are in one of two states: free (E_0) or bound (E), i.e., having recognized and bound a target cancer cell. The role of the cytotoxic cells is to limit the size of the tumor population by recognizing and destroying them. The rate constant for cellular replication of the tumor cells is λ_i . The recognition-binding process of the X population cells by the E_0 effector cells (rate constant k_1) is followed [11] by the lysis of the former and the dissociation of the complex E into E_0 and some non-replicating cellular product P (rate constant k_2). The total number of effector cells is assumed constant in time (for a justification of this and other assumptions see [7]). Schematically, the above mechanisms can be represented as follows



As far as the various parameter domains are concerned, we will be guided by the detailed and well-justified data in [11]. Thus, we consider (using specific values in these ranges for later estimates)

- (i) $0.2 \text{ day} < \lambda_i < 1.5 \text{ day}$;
 - (ii) $10^{-2} < \beta < 10$;
 - (iii) $10^{-1} < \theta_i < 5$;
 - (iv) $0.1 < k_1 N, \quad k_2 < 20$
- } see Section 2

(where $N \equiv 10^6 \text{ cells/mm}^3$ for solid cancers).

Lefever and Garay [11] also noted that the scale of increasing cytotoxic activity for different active effector cells is: activated macrophages < immune T-lymphocytes and natural killer cells < allosensitized T lymphocytes (corresponding to the above parameter ranges).

In what follows, we set up the dimensionless forms of the basic balance equation for each i (Section 2); describe the homogeneous steady states (Section 3); examine travelling wave solutions linking steady states (Section 4); discuss specific analytic solutions (Section 5); establish criteria for phase coexistence and nucleation (Section 6); and investigate critical domain size for tumoral state outbreaks (Section 7).

A concluding discussion in Section 8 precedes three brief appendices on local stability of equilibria; the summary of rigorous results for one-dimensional systems and a description of the means by which the existence of travelling wave solutions is established for Fisher's equation.

2. BALANCE EQUATIONS

For the population density of malignant cells, X , the governing equation is

$$\frac{\partial X}{\partial t} = \dot{X} = \lambda_i f_i(X) - k_1 E_0 x + D \frac{\partial^2 X}{\partial \hat{r}^2}, \quad i = 1, 2, 3, 4, \quad (1)$$

where D is the coefficient of diffusion and λ_i is a rate constant for the corresponding $f_i(X)$. These functions are chosen for their analytic simplicity in reproducing qualitative features that we might expect different types of growth factor to possess. Specifically,

$$f_1(X) = X \left(1 - \frac{X}{N_1} \right), \quad (2)$$

where N_1 is a "local" saturation limit or carrying capacity (see below). Thus, f_1 represents a logistic type growth rate, and represents a "normal" growth term. The growth rate term corresponding to "activation" is

$$f_2(X) = X \left(1 - \frac{X^2}{N_2^2} \right), \quad (3)$$

where again, N_2 represents a local carrying capacity. For growth rate inhibition (compared to normal)

$$f_3(X) = X \left(1 - \frac{X}{N_3} \right)^2, \quad (4)$$

while a fourth case, a hybrid which will be referred to as "inhibition-activation" or "delayed activator," is generated by

$$f_4(X) = \frac{X^2}{N} \left(1 - \frac{X}{N_4} \right), \quad (5)$$

where N is a population that is for now arbitrary. The quantity $f_4(X)$ is qualitatively similar to a class of activator-inhibitor profiles that have been discussed elsewhere [18,19], but is simpler to discuss analytically. Four related functions $g_i(X)$ are shown in Figure 1 for the *same* value of N_i , $N_i = 2$, $i = 1, 2, 3, 4$. In general, the N_i will be different, and this will be assumed except where otherwise stated. Figure 1 shows clearly the reasons for labelling the growth rates $f_i(X)$ as "activator," "normal," etc.

The equation for the population density E_0 of free cytotoxic cells is

$$\dot{E}_0 = -k_1 E_0 X + k_2 E. \quad (6)$$

Since lysis is expected to be much faster than the other processes in the volume element considered [8], the quasi-steady state approximation $\dot{E}_0 \equiv 0$ is invoked, implying

$$E = \frac{k_1 E_0 X}{k_1 X + k_2} \quad (7)$$

whence equation (1) becomes

$$\dot{X} = \lambda_i f_i(X) - \frac{k_1 k_2 E_0 X}{k_1 X + k_2} + D \frac{\partial^2 X}{\partial \hat{r}^2}. \quad (8)$$

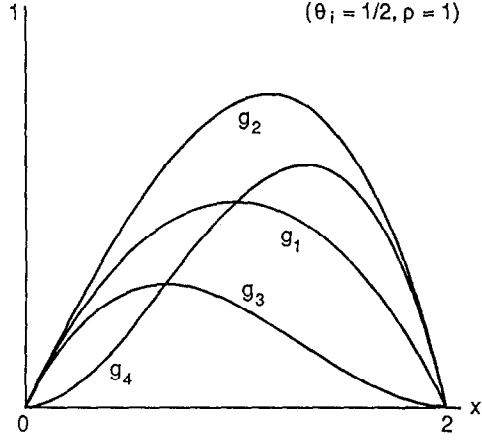


Figure 1. The terms $g_i(x)$, $i = 1, 2, 3, 4$, corresponding to the special case of $\theta_i = \frac{1}{2}$ for all i , $\rho = 1$. In equation (10), these terms correspond respectively to the following growth rate descriptions: normal, activator, inhibitor, delayed activator.

The following changes of variable

$$x = \frac{k_1 X}{k_2}, \quad \tau_i = \lambda_i t, \quad \theta_i = \frac{k_2}{k_1 N_i}, \quad \beta_i = \frac{k_1 E_i}{\lambda_i}, \quad \hat{r} = \left(\frac{D}{\lambda_i} \right)^{\frac{1}{2}} r \quad (9)$$

reduce (8) to

$$\frac{\partial x}{\partial \tau_i} = g_i(x) - \frac{\beta_i x}{1+x} + \frac{\partial^2 x}{\partial r^2}, \quad i = 1, 2, 3, 4, \quad (10)$$

where $g_1(x) = x(1 - \theta_1 x)$ and $g_2(x)$, $g_3(x)$ are obvious modifications of (3) and (4), respectively. The expression for $g_4(x)$ is

$$g_4(x) = \rho x^2(1 - \theta_4 X), \quad (11)$$

where $\rho = k_2/k_1 N$ is a parameter that may take on various values (depending on N), including θ_4 . The population density N can be thought of as modifying the rate constant λ_4 .

The steady state of (10) are solutions of the Hamiltonian type system

$$H = \frac{1}{2} \left(\frac{dx}{dr} \right)^2 + V_i(x), \quad (12)$$

where H is a spatial invariant determined by the boundary conditions chosen, and the "potential energy" or "free energy"

$$V_i(x) = \int_0^x g_i(\alpha) d\alpha - \beta_i x + \beta_i \ln(x+1). \quad (13)$$

The homogeneous steady states of equation (10) are the extrema of $V_i(x)$, which in general admits at most two physically acceptable values. Some examples of $V_i(x)$ are shown in Figure 2. Since it is important to understand the homogeneous problem for a given i in (10), being intimately related to the full problem, the next section is devoted to a study of the homogeneous steady states of (10), i.e.,

$$g_i(x) = \frac{\beta_i x}{1+x}, \quad i = 1, 2, 3, 4. \quad (14)$$

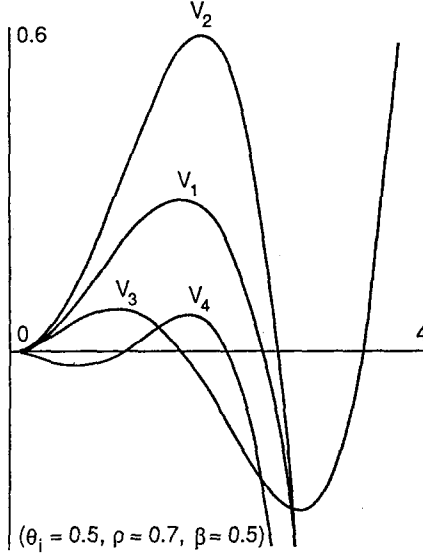


Figure 2. The "free energy" functions, $V_i(x)$, $i = 1, 2, 3, 4$, defined by equation (13), corresponding to the growth rate functions $g_i(x)$.

3. HOMOGENEOUS STEADY STATES (x_s) (SEE APPENDIX 1)

3.1. $i = 1$: Normal Growth Rate

(From now we drop the subscript i when the context permits this.) This case has been discussed elsewhere in the literature [8], so we content ourselves with merely stating the existence and linear stability results. We refer to the situation when $x_s = 0$ as the null tumoral or "cancer free" state. Clearly, this exists for all values of θ_1 and β_1 . However, this cancer-free state is unstable for $\beta < 1$; it is stable for $\beta > 1$. The non-zero steady state for $\theta > 1$ is given by

$$x_s(\beta) = \frac{1 - \theta + \sqrt{(1 + \theta)^2 - 4\theta\beta}}{2\theta}. \quad (15)$$

This exists only for $\beta < 1$ (see Figure 3a). In terms of the quantity β_c , where

$$\beta_c = \frac{(1 + \theta)^2}{4\theta}, \quad (16)$$

this steady state is stable with respect to small departures from x_s .

If $\theta < 1$, there exists for $\beta \in (1, \beta_c)$ the phenomenon of bistability: two non-zero (i.e., cancerous) steady states exist (see Figure 3a). The upper branch in $(0, \beta_c)$ is stable, the lower is unstable. If $\beta < 1$, only the stable upper branch is present. If $\beta > \beta_c$, we recover the stable cancer-free state only. The bistability is defined by

$$x_s(\beta) = \frac{1 - \theta \pm 2\sqrt{\theta(\beta_c - \beta)}}{2\theta}. \quad (15')$$

3.2. $i = 2$: Activator

The steady states are solutions of

$$x \left\{ 1 - \theta^2 x^2 - \frac{\beta}{1 + x} \right\} = 0. \quad (17)$$

As in all four cases, the cancer-free state is unstable for $\beta < 1$ and stable for $\beta > 1$. The tumoral state(s) satisfy the cubic equation

$$\beta = -\theta^2 x^3 - \theta^2 x^2 + x + 1. \quad (18)$$

Extrema of $\beta(x)$, defined by $\beta'(x) = 0$, correspond to only one positive steady state extremum

$$x_s = \frac{\sqrt{\theta^2 + 3} - \theta}{3\theta} \quad (19)$$

regardless of the value of $\theta \neq 0$. For $\beta < 1$ there is only the null solution; for $\beta \in (1, \beta_c)$ there are two non-null branches, and again none for $\beta > \beta_c$. Here, for $i=2$, β_c is defined as

$$\beta_c = \frac{2}{27\theta} \left\{ (\theta^2 + 3)^{3/2} + 9\theta - \theta^3 \right\}. \quad (20)$$

As in the previous case, the upper branch in $(0, \beta_c)$ is stable, the lower branch in $(1, \beta_c)$ is unstable (see Figure 3).

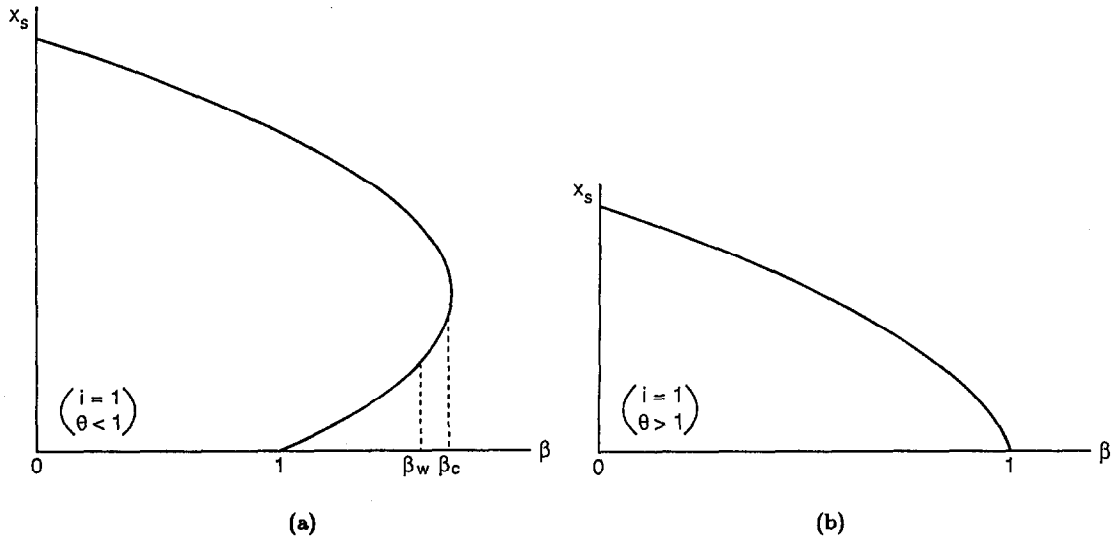


Figure 3. Steady states $x_s(\beta)$ for the case $i = 1$: (a) $\theta_1 < 1$, (b) $\theta_1 > 1$. Figure 3(a) is also qualitatively valid for $i = 2$, and all θ_2 .

3.3. $i = 3$: Inhibitor

The cancer free state $x_s = 0$ has the same stability properties as the two previous cases. The tumoral states satisfy the cubic equation

$$\beta = \theta^2 x^3 + \theta(\theta - 2)x^2 + (1 - 2\theta)x + 1. \quad (21)$$

Proceeding as in Section 3.2, the steady state extrema are given by solutions of $\beta'(x_s) = 0$, yielding the roots $x_{s2} = 1/\theta$ and $x_{s1} = (1 - 2\theta)/3\theta$. Clearly, for $\theta > 1/2$ there is only one positive extremum. The values of β corresponding to x_{s1} and x_{s2} respectively are

$$\beta = \beta_c = 1 + \frac{1}{27\theta} (4 + \theta)(1 - 2\theta)^2 \quad (22)$$

and $\beta = 0$ (see Figure 4a).

Linear stability analysis applied to the spatially homogeneous version of (10) reveals that both the upper ($x_s > x_{s2}$) and lower branches ($0 < x_s < x_{s1}$) are unstable and the middle branch ($x_{s1} < x_s < x_{s2}$) is stable (see Appendix 1).

3.4. $i = 4$: Delayed Inhibitor

In this case, the cancer-free state is stable for all $\beta > 0$. The non-zero steady states satisfy the cubic equation

$$\hat{\beta} = \frac{\beta}{\rho} = -\theta x^3 - \theta x^2 + x^2 + x. \quad (23)$$

There is only one positive steady state x_s :

$$x_s = \frac{1 - \theta + \sqrt{(1 - \theta)^2 + 3\theta}}{3\theta} \quad (24)$$

regardless of the value of non-zero θ . For $0 < \hat{\beta} < \hat{\beta}_c$, there are two branches for x_s , and none for $\hat{\beta} > \hat{\beta}_c$. Here, $\hat{\beta}_c$ is defined as (see Figure 4b)

$$\hat{\beta}_c = \alpha^*(1 + \alpha^*)(1 - \theta_4 \alpha^*),$$

where

$$\alpha^* = \frac{1 - \theta_4 + \sqrt{(1 - \theta_4)^2 + 3\theta_4}}{3\theta_4}.$$

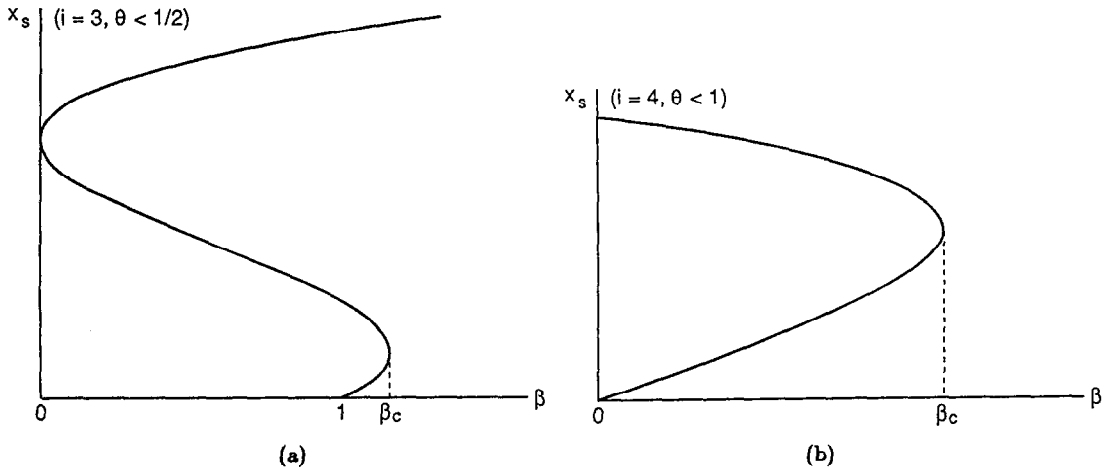


Figure 4. Steady states $x_s(\beta)$: (a) $i = 3, \theta_3 < \frac{1}{2}$. If $\theta_3 > \frac{1}{2}$, there is only one positive extremum for $\beta(x_s)$: the graph is then qualitatively like that for $i = 1, \theta_1 < 1$.

By following the “evolution” of the steady states of the homogeneous systems as functions of β , in particular, we are able to infer the qualitative shapes of the $m_i(x)$ in equation (10), where

$$m_i(x) = g_i(x) - \frac{\beta_i x}{1 + x}, \quad i = 1, \dots, 4, \quad (25)$$

(see Figure 5).

Of course, the behavior of $m_i(x)$ is easily calculated for given β_i, θ_i etc., but all that is required here is information on the qualitative behavior of the steady states. This information will then be used to discuss the existence of waves of translation occurring between cancerous and non-cancerous regimes in inhomogeneous media (Section 4).

As will be seen below, there are four basic types of behavior for the $m_i(x)$: one type can evolve into another as β varies for a given label i , so in this sense these four classes, (denoted in Figure 6 by Classes I, II(a), II(b) and III) are more fundamental in a descriptive sense in this context. In each case, $m_i = 0$ when $x = 0$, and $x = x_1$. Additionally $m_i = 0$ when $x = x_2$ in Cases II(a) and II(b), and $m_i = 0$ when $x = x_3$ in Case III. Recall that each point $(0,0)$ and $(x_j, 0)$, $j = 1, 2, 3$, is linearly stable or unstable respectively according to whether $m'_i(x)$ is < 0 or > 0 there.

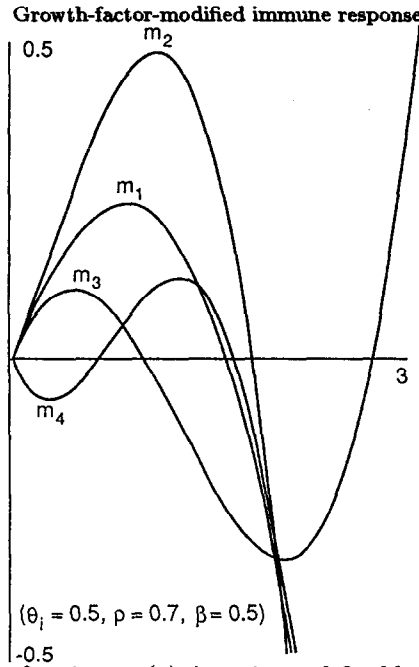


Figure 5. The functions $m_i(x)$, $i = 1, 2, 3, 4$, defined by equation (25).

Consider now the “normal” system $i = 1$ corresponding to $m_1(x)$. Since the $x_s - \beta$ diagram for $\theta > 1$ is topologically equivalent to the case for $\theta < 1$ when $\beta < 1$, we refer to Figure 3b only in our discussion here. Thus, for $\beta \in (0, 1)$, $m_1(x)$ is in Class I. This changes for $\beta \in (1, \beta_c)$ so that $m_1(x)$ is in Class II(a). There are no non-trivial steady states for $\beta > \beta_c$. An identical description applies to the activator case $i = 2$, corresponding to $m_2(x)$ (but recall that $\beta_c(\theta)$ varies from $i = 1$ to $i = 4$). The inhibitor system $i = 3$ gives the most complicated form of $m(x) = m_3(x)$ considered here. There are two non-null steady states for $\beta \in (0, 1)$, whence $m_3(x)$ is in Class II(b). When $\beta \in (1, \beta_c)$, there are three such steady states, two of which are unstable, so $m_3(x)$ is now in Class III. Finally, for the activator-inhibitor case ($i = 4$), $m_4(x)$ is in some sense “close” to Class II(a) for $\beta \in (0, \beta_c)$; note that linear analysis indicates marginal or neutral stability for the null state $x_s \equiv 0$.

4. TRAVELLING WAVE SOLUTIONS

We now seek travelling wave solutions linking steady-states (stable-stable or stable-unstable): of particular interest here is the possibility of a non-zero cancerous state replacing a cancerous one (or vice versa). In equation (10) set

$$x(r, \tau_i) = \phi(\xi), \quad \xi = r - c\tau_i, \quad (26)$$

so that ϕ satisfies the equation

$$\phi'' + c\phi' + m_i(\phi) = 0. \quad (27)$$

In the phase plane (ϕ, η) defined by the equations

$$\begin{aligned} \phi' &= \eta \\ \eta' &= -c\eta - m_i(\phi) \end{aligned} \quad (28)$$

$(0, 0)$ and $(\phi_j, 0)$, $j = 1, 2$, or 3 , (depending on which Classes I–III are relevant) are the singular points corresponding to the x_j , $j = 1, 2, 3$. Away from these points,

$$\frac{d\eta}{d\phi} = -\frac{(c\eta + m_i(\phi))}{\eta}. \quad (29)$$

Linearizing about the singular points (see [20]) enables them to be classified in the usual way based on the characteristic equation

$$\lambda^2 + c\lambda + m'_i(\phi_j) = 0, \quad j = 0, 1, 2, 3 \quad (30)$$

(where $\phi_0 \equiv 0$), for each i .

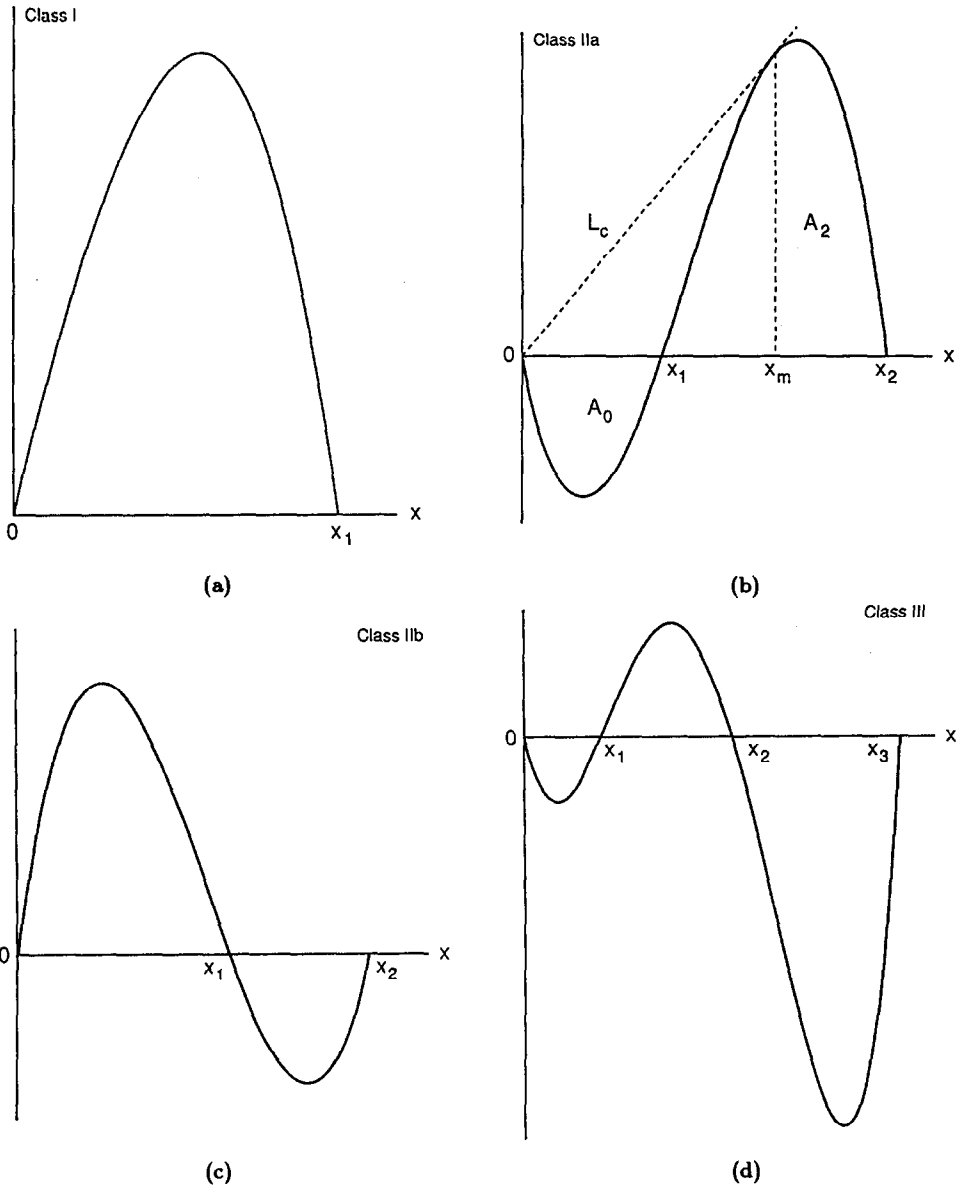


Figure 6. The set of basic functional types defining the basic behavior of the functions $m_i(x)$; for a given i , $m_i(x)$ can evolve through some of these types as the set (β, θ_i) varies. Class I: $x = 0$ is unstable, $x = x_1$ is stable. Class II(a): $x = (0, x_1, x_2)$ are stable, unstable, stable respectively. (For explanation of other features see Sections 4 and 7). Class II(b): the complement of Class II(a). Class III: $x = (0, x_1, x_2, x_3)$ are stable, unstable, stable, unstable respectively.

In Table 1, we also identify the classes into which the singular points fall (dropping the subscript i).

Note that if $c < 0$ (i.e., wave travels to the left), then all the stable nodes and spirals change their stability while retaining their type, and the saddle points are unchanged.

As pointed out by Murray [20] in his summary of insect population control, there are a number of travelling wave possibilities for various ranges of c . A rigorous account of many of the possibilities can be found in [21]. A brief summary of related theorems can be found in Appendix 2.

As noted in [20], we can divide the phase plane into various domains and examine the trajectories between adjacent singular points. Let us consider some (but not all) of the possible situations, focusing for the present on Cases I, II(a) or II(b).

Table 1.

Singular point	Sign of $m'(\phi_j)$	Class	Classification
(0,0)	$\frac{c^2}{4} > m'(0) > 0$	I, II(b)	Stable node
	$m'(0) > \frac{c^2}{4}$	I, II(b)	Stable spiral
	$m'(0) < 0$	II(a), III	Saddle point
$(\phi_1, 0)$	$\frac{c^2}{4} > m'(\phi_1) > 0$	II(a), III	Stable node
	$m'(\phi_1) > 0$	II(a), III	Stable spiral
	$m'(\phi_1) < 0$	I, II(b)	Saddle point
$(\phi_2, 0)$	$\frac{c^2}{4} > m'(\phi_2) > 0$	II(b)	Stable node
	$m'(\phi_2) > \frac{c^2}{4}$	II(b)	Stable spiral
	$m'(\phi_2) < 0$	II(a), III	Saddle point
$(\phi_3, 0)$	$\frac{c^2}{4} > m'(\phi_3) > 0$	III	Stable node
	$m'(\phi_3) > \frac{c^2}{4}$	III	Stable spiral

Suppose that $c^2 > 4m'(0) > 0$ (Cases I and II(b)) and hence $m'(\phi_1) < 0$. Then, $(0,0)$ is a stable node and $(\phi_1, 0)$ is a saddle point. This region of the phase plane is topologically equivalent to that for Fisher's equation (see [20,21]). It is well-known, and can be shown using standard arguments (see Appendix 3) that a monotone solution $\phi(\xi)$ exists for all wave speeds $c \geq 2[m'(0)]^{\frac{1}{2}}$ such that $\phi(-\infty) = \phi_1$ and $\phi(\infty) = 0$. For any $c \geq c_{\min}$, there exists a trajectory connecting the saddle point $(\phi_1, 0)$ to the stable node $(0,0)$. This corresponds to waves propagating the steady cancerous state $\phi = \phi_1$ to the unsteady null state $\phi = 0$.

In a similar fashion, other domains admit travelling wave solutions. Examination of equation (29) away from the singular points enables a comprehensive description of the phase plane to be found (see Figure 7). In particular, we note that the sign of $\frac{d\eta}{d\phi}$ changes from positive to negative if for some c , $m_i(\phi) = -c\eta$. If both c and η are positive, this restricts us to the domain (ϕ_1, ϕ_2) in Case II(b), whence a possible set of wavefront solutions exist joining $\phi(-\infty) = \phi_1$ and $\phi(\infty) = \phi_2$ in a *non-monotonic* fashion.

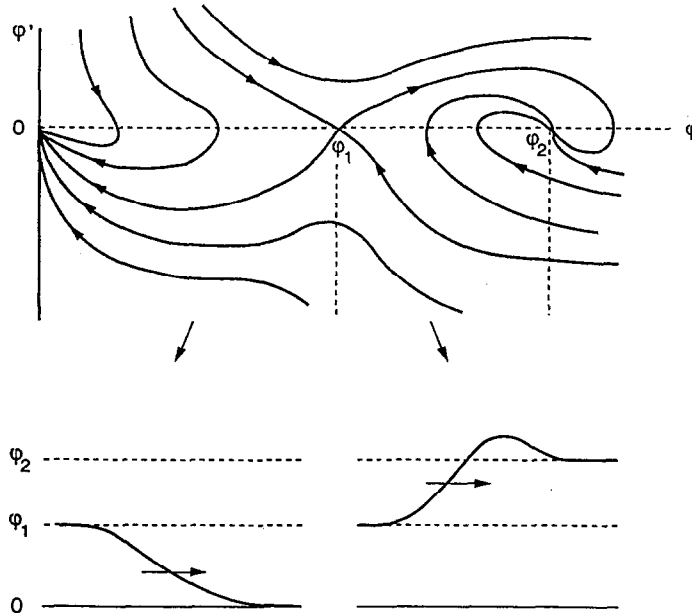


Figure 7. Possible phase portrait for $c^2 > 4 \max[m'(0), m'(\phi_2)]$, corresponding to Class II(b) behavior (Figure 6c). The points $(0,0)$ and $(\phi_2, 0)$ are stable nodes; $(\phi_1, 0)$ is a saddle point. The steady states, $x_s = 0, x_2$, are unstable and x_1 is stable in this class. Underneath are shown the corresponding possible wavefront solutions for restricted domains. (This figure is based on Figure 11.8 in [20].)

The Cases II(a) and III correspond to saddle points at $(0, 0)$ and $(\phi_2, 0)$ separated by a stable node $(\phi_1, 0)$ (provided $c^2 > 4m'(\phi_1)$). By studying the eigenvalues and corresponding eigenvectors for this situation, and by utilizing continuity arguments with $m'(0)$ and $m'(\phi_2)$ in appropriate ranges, it can be inferred that there is a unique value of c , c_* say, such that there is a trajectory joining the saddle points $(0, 0)$ and $(\phi_2, 0)$. This corresponds to a wave moving with unique speed c_* propagating the stable cancerous state $\phi(-\infty) = \phi_2$ to the stable non-cancerous state $\phi(\infty) = 0$. The value of c_* depends on the nonlinear interaction term $m_i(\phi)$. Note that similar considerations also apply to the states ϕ_1 and ϕ_2 , except that $(\phi_1, 0)$ being a stable node if $c^2 > 4m'(\phi_1)$, implies the existence of waves for all $c \geq 2[m'(\phi_1)]^{\frac{1}{2}}$. These waves carry the stable cancerous state ϕ_2 to the unstable cancerous state $\phi_1 < \phi_2$. It is a form of this transition that corresponds to an outbreak in the budworm infestation problem [20]. Case III further allows the possibility of waves carrying states ϕ_2 into ϕ_3 . Clearly other possibilities exist depending on the sign of c .

Specifically, though, we are interested in the situation corresponding to Case II(a): a travelling wave solution linking states $\phi = \phi_2$ and $\phi = 0$. The details below carry over, in particular, to Case III, but also to the other cases when modified appropriately.

Since

$$\lim_{\xi \rightarrow \pm\infty} \phi'(\xi) = 0, \quad \lim_{\xi \rightarrow -\infty} \phi(\xi) = \phi_2, \quad \lim_{\xi \rightarrow \infty} \phi(\xi) = 0, \quad (31)$$

we have from (27),

$$\begin{aligned} c \int_{-\infty}^{\infty} (\phi')^2 d\xi &= - \int_{-\infty}^{\infty} m_i(\phi) \phi' d\xi \\ &= \int_0^{\phi_2} m_i(\phi) d\phi, \end{aligned} \quad (32)$$

thus establishing that c takes on the sign of $\int_0^{\phi_2} m_i(\phi) d\phi$, the wave being stationary if this integral is zero. Recalling (13) and (25), it is clear that

$$c \begin{array}{l} > \\ < \end{array} 0 \text{ if } [V_i(x)]_0^{x_2} \begin{array}{l} > \\ < \end{array} 0 \quad (33)$$

respectively, i.e., the wavefront moves to the right if the “free energy” V_i at $x = x_2$ (or $\phi = \phi_2$) exceeds that at $x = 0$; a corresponding statement of course applies for $c < 0$.

Graphically, $c \geq 0$ is implied by $A_2 \geq A_0$ in Figure 6b. As discussed above, the question arises: under what circumstances can the sign of c become negative? Reference to Figure 6(b) shows that for $c < 0$ we require that the steady states x_1 and x_2 are closer together than are 0 and x_1 (an almost identical situation to this one occurs in the budworm infestation problem). This is accomplished for the “normal” growth rate ($i = 1$) by increasing θ towards 1 for $\beta \in (1, \beta_c)$. This corresponds to either (i) improving the relative efficiency of binding and lysis, or (ii) reducing the local saturation limit N_i ; or some combination of both. Similar considerations also apply to the other three cases. The delineation of the $\beta - \theta$ plane for the normal case into regions for zero, one or two non-null steady states is shown in Figure 8a, with corresponding results for $i = 3$ in Figure 8c.

5. ANALYTIC SOLUTIONS FOR SIMPLIFIED MODELS

In this section, we attempt to gain insight into the wavefront problem by examining a related one with simplified expressions for $m_i(x)$. Specifically, we focus attention on Cases I and II(a), replacing the $m_i(x)$ in each case by an appropriate polynomial. This can be done for Cases II(b) and III also, of course, or in subdomains of interest for these cases.

Case I

Consider the equation

$$\frac{\partial x}{\partial \tau_i} = M_i(x) + \frac{\partial^2 x}{\partial r^2}, \quad (34)$$

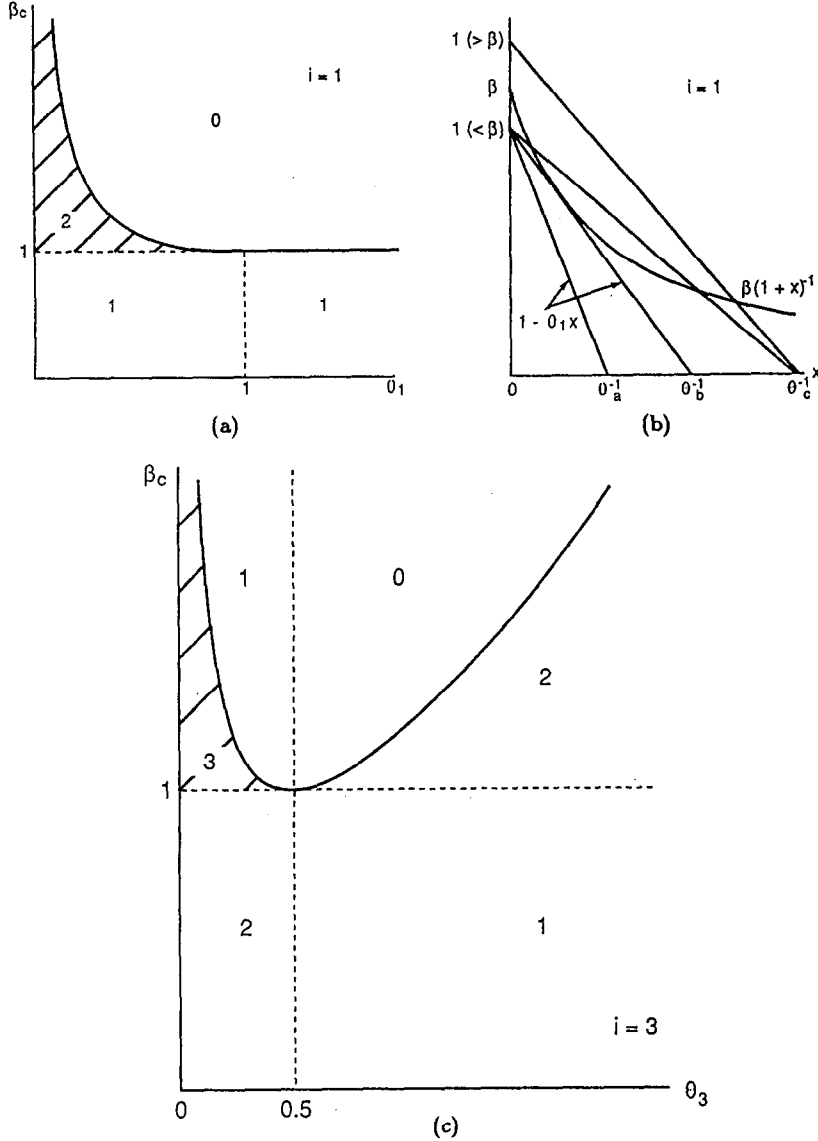


Figure 8. (a) $\beta_c(\theta)$ for the case $i = 1$, delineating the number of non-zero steady states in each region of parameter space (see also Figure 3). This is also illustrated in (b) for $i = 1$, where the existence, location and nature of the roots of $(1 - \theta_1 x) = \beta(1 + x)^{-1}$ are shown for $\beta < 1$ (one root) and $\beta > 1$; for $\theta_1 > \theta_b$ when $\beta > 1$ there are no roots. Similar types of diagram can be drawn for $i = 2, 3$ and 4. That for $i = 3$ is shown in (c) (see also Figure 4).

where

$$M_i(x) = m'_i(0)x \left(1 - \frac{x}{x_1}\right). \quad (35)$$

$M_i(x)$ is a parabola mimicking the form of $m_i(x)$ on $[0, x_1]$, i.e., $M_i = m_i = 0$ at $x = 0, x_1$, and $M'_i(0) = m'_i(0) > 0$. Temporarily introducing another scaling

$$\tau_i^* = m'_i(0)\tau_i, \quad r^* = \sqrt{m'_i(0)}r, \quad (36)$$

(34) readily reduces to the canonical form for Fisher's equation for the variable $\hat{X} = x/x_1$:

$$\frac{\partial \hat{X}}{\partial \tau_i^*} = \hat{X}(1 - \hat{X}) + \frac{\partial^2 \hat{X}}{\partial r^{*2}}. \quad (37)$$

This has an exact travelling wavefront solution [20]

$$\hat{X}(r^*, \tau_i^*) = \phi(r^* - c\tau_i^*) = \phi(\xi),$$

where

$$\phi(\xi) = \{1 + (\sqrt{2} - 1)e^{\xi/\sqrt{6}}\}^{-2}, \quad (38)$$

where the waveform has been selected to satisfy $\phi(0) = \frac{1}{2}$. In dimensionless variables, $c = 5/\sqrt{6} \approx 2.04$. Reverting to the original space and time variables via (36) and (9), we find

$$x(\hat{r}, t) = x_1 \left\{ 1 + (\sqrt{2} - 1) \exp \left[\left(\frac{m'_i(0)\lambda_i}{6} \right)^{\frac{1}{2}} (\hat{r} - \hat{c}t) \right] \right\}^{-2} \quad (39)$$

where

$$\hat{c} = 5 \left(\frac{m'_i(0)\lambda_i D}{6} \right)^{\frac{1}{2}}. \quad (40)$$

This exact solution is one of an infinite set that exist for (dimensionless) $c \geq 2(m'_i(0))^{\frac{1}{2}}$. Murray [20] points out that the analytic solution, when obtained, may not be the most relevant because the quantitative form of the wave may be different from that obtained via asymptotic methods. Indeed, using singular perturbation techniques in the small parameter $\epsilon = c^{-2} \leq 0.25$, Murray demonstrates that the $O(1)$ term in the uniformly valid asymptotic solution \hat{X} for all ξ is

$$\hat{X}(\xi; \epsilon) = (1 + e^{\xi/\epsilon})^{-1}$$

and this term alone is accurate to within a few percent of the computed form. Notwithstanding these words of caution, however, we are primarily interested here in the *speed* of the wavefront, and not its *detailed* functional form. We note from (40) that \hat{c} increases as the square root of each of $m'_i(0)$, λ_i and D .

Case II(a)

In equation (34), we now define M_i as

$$M_i = b x(x_1 - x)(x - x_2), \quad (41)$$

where

$$b = \frac{m'_i(x_1)}{x_1(x_2 - x_1)} > 0 \quad (42)$$

so that $M'_i(x_1) = m'_i(x_1)$.

In dimensional independent variables, the governing partial differential equation is

$$\frac{\partial x}{\partial t} = \lambda_i b x(x_1 - x)(x - x_2) + D \frac{\partial^2 x}{\partial \hat{r}^2}. \quad (43)$$

Following [20,22], we can show that a solution of (43) is

$$x(\hat{r}, t) = \phi(\hat{r} - ct) = \phi(\xi),$$

where

$$\phi(\xi) = \phi_2 \left\{ 1 + \exp \left(\sqrt{\frac{b}{2}} \phi_2 \xi \right) \right\}^{-1} \quad (44)$$

where $\phi(-\infty) = \phi_2$, $\phi(0) = \phi_2/2$, $\phi(\infty) = 0$.

The speed of the wavefront is

$$c = \left(\frac{\lambda_i D b}{2} \right)^{\frac{1}{2}} (x_2 - 2x_1); \quad (45)$$

clearly $c \geq 0$ according as $x_1 \leq x_2/2$ (this result also follows upon replacing m_i with M_i in (32)). The conditions under this may happen to have been discussed earlier. Note that (43) is a form of the reduced Nagumo equation.

In Case I, we have seen that monotone wavefront solutions exist, linking the cancer-free unstable steady state with the stable tumoral steady state $x = x_1$ for all wave speeds $c \geq 2[m'_i(0)]^{\frac{1}{2}} = c_{\min}$. In the original variables the (stable) wavespeed

$$c_{\min} = 2\sqrt{D\lambda_i m'_i(0)}. \quad (46)$$

This situation pertains to the “normal” case ($i = 1$) and the “activator” case ($i = 2$), both for $\beta \in (0, 1)$. Evaluating these cases we find

$$c_{\min} = A_i \sqrt{1 - \beta} \quad (47)$$

for $i = 1, 2, 3$, $A_i = 2\sqrt{D\lambda_i}$. The “delayed inhibitor” case ($i = 4$) also apparently falls into this category, but as we have seen the state $x = 0$ is (linearly) marginally stable, and the wave speed is pure imaginary for all β (as it is for all $\beta > 1$ in the cases $i = 1, 2$ above).

For $\beta \in (0, 1)$, the “inhibitor” case ($i = 3$) is in Class II(b), and by the earlier arguments a wave exists linking the states $(0, 0)$ and $(0, x_1)$ for all $c \geq c_{\min} = A_3 \sqrt{1 - \beta}$. This also applies for $i = 3$ when $\beta \in (1, \beta_c)$ for the steady states $(0, x_1)$ and $(0, x_2)$, (Class III) where now

$$c_{\min} = A_3 \sqrt{m'_3(x_1)} = A_3 \left\{ x_1 \left(x_1 - \frac{1}{\theta} \right) \left(x_1 - \frac{1 - 2\theta}{3\theta} \right) \right\}^{\frac{1}{2}}. \quad (48)$$

Since $0 < x_1 < \frac{1-2\theta}{3\theta}$ for $\beta \in (1, \beta_c)$, clearly we must have $\theta < \frac{1}{2}$ for a real speed c_{\min} .

In Case II(a), we know that a unique wave speed exists joining the stable states $(0, 0)$ and $(0, x_2)$. This class is occupied by both the normal and activator cases ($i = 1, 2$) when $\beta \in (1, \beta_c)$. For comparative purposes we use the exact solution (45) found for the cubic form M_i discussed above, for the cases $i = 1$ and 2. From (42) and (45)

$$c = \left\{ \frac{D\lambda_i m'_i(x_1)}{2x_1(x_2 - x_1)} \right\}^{\frac{1}{2}} (x_2 - 2x_1), \quad (49)$$

where

$$m'_1(x_1) = \frac{2\theta x_1}{(1 + x_1)} \left(\frac{1 - \theta}{2\theta} - x_1 \right), \quad \theta < 1 \quad \text{and} \quad (50)$$

$$m'_2(x_1) = \frac{x_1}{(1 + x_1)} (1 - 2\theta^2 x_1 - 3\theta^2 x_1^2). \quad (51)$$

In each case, $m'_i(x_1) > 0$ for x_1 defined by the restrictions on β .

For reasonable ranges of β, θ_1 (within the restrictions $\beta, \theta_1 < 1$) and θ_2 , we see that with the possible exception of $x_2 - 2x_1$ in (49), all quantities multiplying the A_i in (47) and the $(D\lambda_i)^{\frac{1}{2}}$ in (49) are of order 1. Obviously, β very close to unity, and x_2 very close to $2x_1$ can result in a greatly reduced wave speed, but within the confines of this one-dimensional model we restrict ourselves to noting the functional form of $c(\lambda_i, D, m'_i, x_j)$ and to providing an estimate of it. Since $D \sim 10^{-9} - 10^{-11} \text{ cm}^2/\text{sec}$ for most biological tissues [20], and typically $\lambda_i \sim 1/\text{day}$ [2] we find that $c_{\min} \approx c \sim 2 \times 10^{-7} \text{ cm/sec} - 2 \times 10^{-8} \text{ cm/sec}$. To grow from a single cell to a linear segment of length 1cm. would therefore take $\approx 50-500$ days, depending on the value of D (and assuming for simplicity $\beta = 0$). This latter figure agrees with that derived for the logistic case ($i = 1$) elsewhere [8]. Again, for values of β close to unity, for example, c_{\min} may be reduced by an order of magnitude or more.

6. PHASE COEXISTENCE AND NUCLEATION

The basic differences between the dynamic behavior we have examined here in the phenomenological models $i = 1, 2, 3, 4$ are well exemplified by the differences between the Classes I and II(a). In Category I (corresponding to certain parameter domains for β and θ_i), any initial condition evolves into a progressive "tumor." Outside the domain (for $\beta > \beta_c$ in particular), any tumor initially presented is rejected: only a stable null exists. This last statement is, of course, true for all classes, but once II(a) has been entered, for $\beta \in (1, \beta_c)$ ($i = 1, 2$, and $i = 3$ for Class III), or in case $i = 4$, for $\beta \in (0, \beta_c)$, a unique stable wave solution can exist between appropriate states. The stable steady states correspond to maxima of the "free energy" $V_i(x)$ while the unstable state x_1 corresponds to a minimum of $V_i(x)$.

If the wavefront velocity is zero, the tumoral state and tumor-free state coexist: there exists an inhomogeneous steady state solution corresponding to two semi-infinite phases ($x = 0$ and $x = x_1$, for example) in equilibrium. We have seen that for an idealized model of Case II(a) this will occur if $x_2 = 2x_1$. However, by applying the condition that the "free energies" of the phases are equal, we can arrive at an equivalent but more specific criterion.

Thus,

$$V(0) = V(x_1) \quad (52)$$

implies

$$\beta = \beta_w = \frac{p_i(x_1)}{x_1 - \ln(x_1 + 1)}, \quad i = 1, 2, 3, 4, \quad (53)$$

where

$$\begin{aligned} p_1(x) &= \frac{1}{2}x^2 - \frac{1}{3}\theta_1 x^3, \\ p_2(x) &= \frac{1}{2}x^2 - \frac{1}{4}\theta_2^2 x^3, \\ p_3(x) &= \frac{1}{2}x^2 - \frac{2}{3}\theta_3 x^3 + \frac{\theta_3^2}{4}x^4, \\ p_4(x) &= \frac{1}{3}\rho x^3 - \frac{1}{4}\rho x^4. \end{aligned} \quad (54)$$

As pointed out in [8] where the normal case ($i = 1$) was studied in this domain, the onset of tumor growth is governed by a Maxwell construction (in the language of statistical mechanics), and is analogous to the mechanism of equilibrium first-order phase transitions. For $1 < \beta < \beta_w$, the wave is progressive in favor of the tumoral state ($c > 0$), while for $\beta_w < \beta < \beta_c$ it is regressive ($c < 0$) (see Figure 3a) for $i = 1, 2, 3$. For $i = 4$, $\beta_w \in (0, \beta_c)$.

Clearly this indicates, in simplistic fashion, the efficiency of the immune system characterised by the parameter β . In higher dimensions, the stabilizing effect of the cytotoxic cells becomes more obvious and can induce a nucleation phenomenon (see [22] for a general discussion of nucleation in systems with multiple stationary states). This corresponds here to a spherical tumor (state x_1 in 3 dimensions with spherical symmetry) embedded in an infinite non-tumor region (state 0). Depending on β and θ_i , there will, in general, be a critical radius above which the tumor will grow and below which it will shrink. The effect of diffusion on the "free energy" $V(x)$ plays a role analogous to that of surface tension in the classical nucleation problem [23]. The critical radius corresponds in this one-dimensional treatment to the vanishing of the wavefront velocity discussed above, i.e., the coexistence of two semi-infinite states separated by a planar "boundary" (though the concentration of tumor cells will have a tanh-like behavior in the vicinity of the front (see equation (38))).

Even though this treatment neglects the obvious geometric effects of a spherically symmetric system, we can nevertheless gain an estimate of the size r_n of the "nucleus" by taking the ratio of minimum wave speed to typical growth rate corresponding to a "source" term $m_i(x_1)$, i.e.,

$$r_n \sim \frac{c}{\lambda_i m'_i(x_1)}, \quad (55)$$

but $c \sim \sqrt{\lambda_i D m'_i(x_1)}$, so we may write

$$r_n \sim \sqrt{\frac{D}{\lambda_i m'_i(x_1)}} \sim \frac{D}{c}.$$

From (49), therefore

$$r_n \sim \left\{ \left(\frac{2D}{\lambda_i} \right) \left(\frac{x_1}{m'_i(x_1)} \right) (x_2 - x_1) \right\}^{\frac{1}{2}} (x_2 - 2x_1)^{-1}. \quad (56)$$

Thus, as β varies between 1 and β_w (for the cases $i = 1, 2, 3$) and between 0 and β_w in case $i = 4$, x_1 varies between zero and $x_2/2$. Hence, r_n varies between

$$\left(\frac{2D}{\lambda_i x_2} \right)^{\frac{1}{2}} \lim_{x_1 \rightarrow 0} \left(\frac{x_1}{m'_i(x_1)} \right)^{\frac{1}{2}} \quad (57)$$

and infinity. From Appendix 1, we can infer that $\lim_{x_1 \rightarrow 0} (x_1/m'_i(x_1))^{1/2}$ is $(1 - \theta_i)^{1/2}$, 1 , $\sqrt{3}\theta_i(1 - 2\theta_i)^{-\frac{1}{2}}$ and 1 respectively for $i = 1, 2, 3$ and 4 .

7. CRITICAL DOMAIN SIZE AND POPULATION

An approximate analytical method described in [20] can be utilized to examine the critical size of domain which can sustain an “outbreak” of a tumoral state. The spatially-dependent steady states of (10) are given implicitly by

$$x''(r) + m_i(x) = 0 \quad (58)$$

together with the imposed conditions

$$x(0) = x(L) = 0. \quad (59)$$

By symmetry, the maximum of $x(r)$ can be expected to occur at $r = L/2$. Qualitatively this system, when rescaled to $r \in (0, 1)$, yields a solution like $\sin \pi r$, so (58) implies

$$m_i(x) \approx \frac{\pi^2 x}{L^2}. \quad (60)$$

If x_m is the maximum of x , it can be shown [20] that

$$L = \sqrt{2} \int_0^{x_m} \{F(x_m) - F(\eta)\}^{-\frac{1}{2}} d\eta, \quad (61)$$

where $F(\eta) = \int_0^\eta m_i(\zeta) d\zeta$.

Obviously, x_m is implicitly dependent on L . Schematically, $L(x_m)$ is shown in Figure 9. For $L > L_c$, two solutions $x_m \in (x_1, x_2)$ exist.

As we have noted, x_1 is unstable and x_2 is stable, and in the infinite domain, the state x_2 can be propagated into the cancer free stable state $x = 0$. It is of interest to find L_c such that for $L > L_c$ $x_m \in (x_1, x_2)$. This can be accomplished by considering the approximate result (60). The conditions that must be satisfied for $L = L_c$ are (now regarding (60) as an equation, with $\mu = \pi^2/L_c^2$)

$$\mu x_m = m_i(x_m) \quad \text{and} \quad \mu = m'_i(x_m). \quad (62)$$

These can be solved in principle to yield the pair (L_c, x_m) for each i . This we now do explicitly for $i = 1$ and in implicit form for $i = 2, 3, 4$ (see Appendix 1).

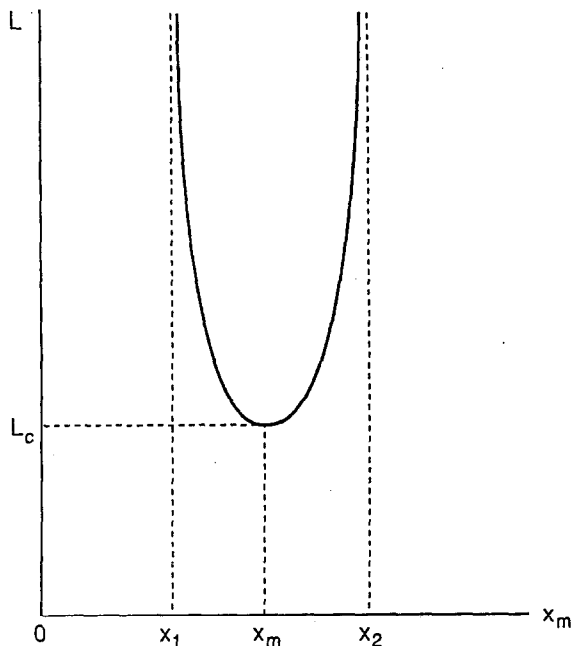


Figure 9. $L(x_m)$, defined by equation (61), plotted schematically. For $L > L_c$ there are two solutions $x_m \in (x_1, x_2)$, and a tumor "outbreak" is likely to be initiated in a finite domain (see also Figure 6b).

$i = 1$

For $x_m \neq 0$ we have, from (62)

$$(1 - \mu) - \theta_1 x_m = \beta(1 + x_m)^{-1}, \quad \text{and} \quad \mu = 1 - 2\theta_1 x_m - \beta(1 + x_m)^{-2}$$

whence

$$x_m = \left(\frac{\beta}{\theta_1}\right)^{\frac{1}{2}} - 1 \quad \text{and} \quad \mu = 1 + \theta_1 - 2(\beta\theta_1)^{\frac{1}{2}}. \quad (63)$$

$i = 2$

$$1 - \mu - \theta_2^2 x_m^2 = \beta(1 + x_m)^{-1}, \quad \text{and} \quad \mu = 1 - 3\theta_2^2 x_m^2 - \beta(1 + x_m)^{-2}$$

yield

$$x_m(x_m + 1)^2 = \frac{\beta}{2\theta_2^2}, \quad \text{and} \quad \mu = 1 - \theta_2^2 x_m^2 \quad (64)$$

$i = 3$

$$1 - \mu - 2\theta_3 x_m + \theta_3^2 x_m^2 = \beta(1 + x_m)^{-1}, \quad \text{and} \quad \mu = 1 - 4\theta_3 x_m + 3\theta_3^2 x_m^2 - \beta(1 + x_m)^{-2}$$

yield

$$(1 + x_m)^2(1 - \theta_3 x_m) = \frac{\beta}{2\theta_3}, \quad \text{and} \quad \mu = 1 - 2\theta_3(1 + 2x_m) + \theta_3^2 x_m(2 + 3x_m) \quad (65)$$

$i = 4$

$$\rho x_m(1 - \theta_4 x_m) - \mu = \beta(1 + x_m)^{-1}, \quad \text{and} \quad \mu = 2\rho x_m - 3\rho\theta_4 x_m^2 - \beta(1 + x_m)^{-2}$$

yield

$$(2\theta_4 x_m - 1)(1 + x_m)^2 = \frac{\beta}{\rho}, \quad \text{and} \quad \mu = 1 + 2\rho x_m(1 - \theta_4) - 3\rho\theta_4 x_m^2. \quad (66)$$

Specifically for case $i = 1$, a choice of $\theta = 0.2$, $\beta = 1.5 < \beta_c$ gives a value of $\mu \approx 0.1$, or $L_c \approx 10$. In the original units, $L_c \approx 10\sqrt{D/\lambda_1} \approx 10^{-2}\text{cm} - 10^{-1}\text{cm}$, depending on which value of D (10^{-11} or $10^{-9}\text{cm}^2/\text{sec}$) is used. The corresponding value of x_m is $x_m \approx 2$ or in the original units $X = k_2x/k_1 \approx 2N\delta$ where δ , estimated from data in [24] varies approximately between 0.2 and 2; N is the total number of neoplastic and normal cells per unit volume. For solid cancers, $N \approx 10^6\text{ cells/mm}^3$ [25], so these values of δ give plausible estimates of maximum cell population densities of the order of N . Clearly, even for small mammals, the typical organ size exceeds the range for L_c above (based on the stated range for D) and so the tumor “outbreak” is likely to be sustained. Once again we anticipate similar orders of magnitude from the remaining three cases, by virtue of the considerations in the previous section.

8. DISCUSSION

We have examined in detail the dynamic behavior of a one-dimensional “tissue system” that supports spatially non-homogeneous perturbations to equilibrium states in the presence of growth-factor-modified immune response. While the functional forms for the growth factor response (characterized here as deviations from the normal logistic-type growth rate) are probably clinically over-simplistic, their analytic simplicity and overall properties render them extremely appropriate for models of this type. Thus, it is to be hoped that the four categories considered here ($i = 1$, normal; $i = 2$, activator; $i = 3$, inhibitor, $i = 4$, delayed activator) in some sense “span” the range of required activation/inhibition behavior, at least at this level of description.

A convenient and evocative description of the steady states of the governing partial differential equation can be made in terms of the so-called free energy function $V_i(x)$, extrema of which define the homogeneous states of the system (see Figure 10). This function is of particular importance in the study of phase coexistence of tumoral/non-tumoral regimes and subsequent nucleation in dimensions greater than one.

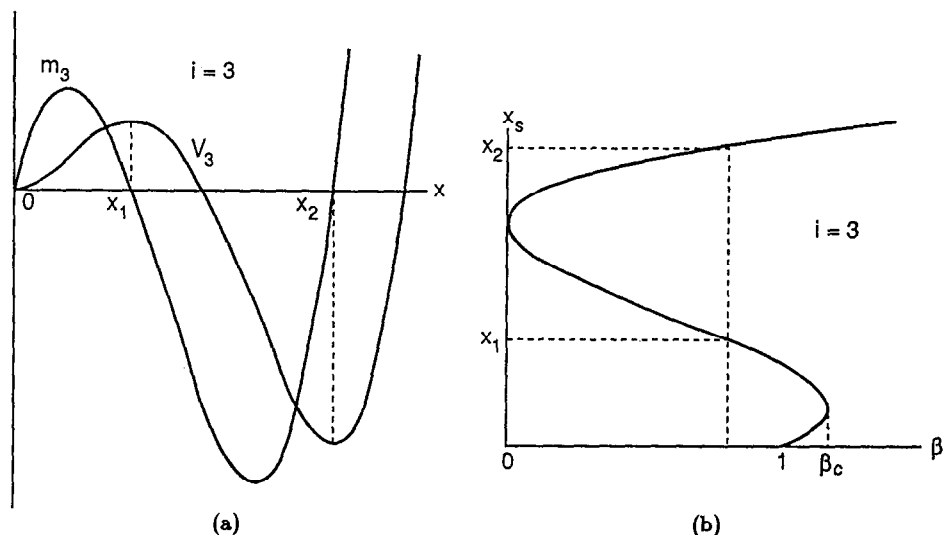


Figure 10 (a): The relationship between the free energy function $V_i(x)$ and $m_i(x)$, illustrated here for $i = 3$ and $0 < \beta < 1$. (b): the corresponding stable state x_1 and unstable state x_2 .

Phase-plane analysis of the governing equations yields the likelihood (under appropriate conditions) of travelling wavefront solutions, carrying one stable steady state into another stable or unstable one. Lower bounds on the wave speeds have been obtained in standard fashion. The wave can be progressive ($c > 0$) or regressive ($c < 0$) depending on the available difference of free energy $V_i(x)$ between the steady states, and in principle the sign of c can change as the various biological parameters are modified appropriately. Analytic solutions for the waveform and speed have been obtained for approximate “source terms” in the governing equations and this provides insight into the dependence of the wave speed on the location of the steady states. Estimates

of wave speeds are made for a certain range of diffusion coefficient, as are estimates (neglecting spherical geometric effects) of a tumor "nucleus" at coexistence. A finite domain is also briefly examined to estimate the system size above which a tumoral "outbreak" may be sustained (and below which it will be rejected). Certainly for most systems of biological interest (within the limitations of the model) it appears that the criterion for this is generally satisfied.

As is frequently the case in mathematical modeling [25], a simplified one dimensional model can give useful insights and parameter limitations for a more realistic fully three-dimensional problem. Many of the characteristics of the simpler system are present in more complex form (usually modified by geometric factors). However, there is a limitation that needs to be noted: the spherically symmetric radial version of equation (10) will contain an additional term $2r^{-1} (\frac{\partial x}{\partial r})$ on the right-hand side. This will preclude in general the existence of plane wave solutions $\phi(r - ct_i)$ for constant c . However, although $c = c(r)$ in general it is clear that for sufficiently large r (provided that $x(r)$ can be considered "slowly varying" in some appropriate sense) this term will become small compared to the others, at least away from the zeros of $m_i(x)$. Under these circumstances one might be justified in seeking such wavefront solutions, although careful analysis would have to be carried out in the neighborhood of the steady states where in fact $m_i(x)$ does vanish.

There is an alternative, somewhat indirect way of gaining insight into this problem. Consider the dimensional equation (8) written in the following form

$$\frac{\partial X}{\partial t} = \lambda_i M_i(X) + D \nabla^2 X \quad (67)$$

where $\nabla^2 \equiv r^{-n} \frac{\partial}{\partial r} (r^n \frac{\partial}{\partial r})$, $n = 0, 1, 2$. Linearizing about $X = 0$ gives,

$$\frac{\partial X}{\partial t} = \lambda_i M'_i(0) X + D \nabla^2 X. \quad (68)$$

We have already noted that in one dimension ($n = 0$), a progressive wave of the form $X(r, t) = \phi(r - ct) = \phi(\xi)$ must satisfy

$$D\phi'' + c\phi' + a\phi = 0, \quad (69)$$

where $a = \lambda_i M'_i(0)$.

A necessary and sufficient condition for a non-negative solution ϕ to exist is that $c^2 \geq 4aD$ (there being no restriction if $a \leq 0$). However, the fundamental solution to (68) for a unit delta function source at the origin is

$$X(r, t) = \frac{1}{(4\pi Dt)^{n/2}} \exp \left\{ at - \frac{r^2}{4Dt} \right\}, \quad (70)$$

so corresponding to a particular cancer cell density $\bar{X}(r, t)$, it must follow that

$$\frac{r^2}{t^2} = 4Da - 2Dn \frac{\log t}{t} - \frac{\text{constant}}{t}. \quad (71)$$

We may associate a "wave" of advance of the initial population with speed arbitrarily close to $2\sqrt{Da} = 2\sqrt{\lambda_i M'_i(0)D}$ for sufficiently large times. Note that (71) only depends weakly (i.e., in the asymptotic correction) on n .

As noted by Kendall [26], even when $a < 0$, the quantity $2\sqrt{Da}$ still carries the connotation of a wave of advance. For given r , the maximum cell population will occur when (omitting the algebraic manipulations from (70))

$$\frac{r^2}{t^2} = 4D|a| + \frac{2nD}{t}. \quad (72)$$

Again, the maxima move outward from the origin with speed asymptotically equal to $2\sqrt{\lambda_i |M'_i(0)|D}$.

It is also important to note that for the range of diffusion coefficient values ($10^{-11} - 10^{-9} \text{ cm}^2/\text{sec}$) the effects of the “reaction” terms $m_i(x)$ are considerable. It has already been noted in Section 5 that a tumoral perturbation may grow to a size of 1 cm in as little as 50–500 days: this compared to a pure diffusion timescale of $L^2/D \sim 10\text{--}1000$ years!

The present model does not include in its kinetics the transformation of normal into neoplastic cells [27] (due to environmental carcinogenic agents, for example), or the effects of environmental fluctuations on bistability. This latter feature has been discussed using stochastic methods for the case $i = 1$ in [11]. The extent to which the existence of microcancer states (induced by external carcinogenic agents) are affected by fluctuating environments for the other cases ($i = 2, 3, 4$) is a topic for further study [28].

A further point remains. It is possible that a class of spatially periodic waves, perhaps themselves unstable, exist, and oscillate around the unstable steady states [2]. They would appear as Hopf bifurcations around $\beta = 1$ and $\beta = \beta_c$ for $i = 1, 2, 3$; and around $\beta = 0$ and $\beta = \beta_c$ for $i = 4$. Just what significance they may have for the biological problem remains an open question: they may, for example, be a means by which a non-trivial unstable state is “dismantled” en route to a stable equilibrium, or they may correspond to a bulk oscillation of the type discussed in [12].

The $x_a - \beta$ plots for $i = 1$ to $i = 4$ have a number of qualitative features in common. With the exception of $i = 3$ ($\theta < \frac{1}{2}$), there are one or two non-zero steady states (depending on θ and β), and even in this exceptional case we may limit ourselves to $0 \leq x_s \leq \theta_3^{-1}$ and obtain a similar configuration to the others. However, $g_3(x)$ is the only member of the $g_i(x)$ that is non-negative for $x > \theta_3^{-1}$, and that is why the upper branch appears in Figure 4(a). In this régime of course, the label “inhibitor” becomes inappropriate, as does the association of θ_3^{-1} , with a local saturation level. Nevertheless, as noted earlier, growth factors are multifunctional [15], and the same cells exposed to their influence at different concentrations may respond in very different ways (for a simple model of this phenomenon, see [18]). Hence, it may be that the case $i = 3$ in this paper is more representative and useful in this context (being richer in structure) than the remaining cases.

Finally, we note the consequences of a simple modification to the logistic growth term for the case $i = 1$. Suppose that a growth factor, produced by the cancer cells, causes an increase in the local saturation level θ_1 , i.e., $\theta_1 = \theta_1(x)$, a monotone increasing function of x . This is entirely plausible, since it is known that tumors are capable of manipulating their environment to their own advantage [29]. Again, suppose for simplicity that (dropping the subscript 1)

$$g(x) = x \left(1 - \frac{\theta x}{1 + a \theta x} \right), \quad (73)$$

where $0 \leq a < 1$, so $g(0) = g([\theta(1-a)]^{-1}) = 0$.

The homogeneous steady states are now solutions of $m(x) = g(x) - \frac{\beta x}{1+x} = 0$, i.e.,

$$\theta(1-a)x^2 + \{\theta(1-a) + \beta a \theta - 1\}x + \beta - 1 = 0. \quad (74)$$

Qualitatively, the $x_s - \beta$ plots are similar to those in Figures 3(a) and 3(b); however, for $\theta < 1$, β_c increases as a increases from zero, as does the location of the x_s intercept, corresponding to the growth-factor modified saturation limit $[\theta(1-a)]^{-1}$. Thus, the range of β over which two non-zero roots exist is extended away from $\beta = 1$. The stability properties of the branches are the same as those for $a = 0$, and $m'(0) = 1 - \beta$ as before, so the minimum wave speed for the $\phi_1(x_1)$ state to be propagated is unchanged. However, referring to equation (49), note that, since x_2 is more sensitive to changes of a than is x_1 (observed from $\beta(x; a)$ defined by (74)), the effect on the wave speed may be dominated by either of the factors $(m'(x_1))^{\frac{1}{2}}$ or $(x_2 - 2x_1)(x_2 - x_1)^{-\frac{1}{2}}$, where

$$m'(x) = 1 - \beta(1+x)^{-2} - \theta x(2 + a \theta x)(1 + a \theta x)^{-2}. \quad (75)$$

The roots x_1 and $x_2(> x_1)$ are the appropriate roots of equation (74). The magnitude of the last term in (75), for given x , is smaller when $a \neq 0$ than when $a = 0$, while as a increases, x_2 greatly exceeds x_1 . In each case, therefore, we anticipate that the wave speed will in general increase as the local saturation level increases.

REFERENCES

1. J. Cairns, The cancer problem, *Sci. Amer.* **233**, 64–74 (1975).
2. R. Lefever and R.P. Garay, A mathematical model of the immune surveillance against cancer, In *Theoretical Immunology* (Edited by G.I. Bell, A.S. Perelson and G. Pimbley), Chapter 17, pp. 481–518, Marcel Dekker, New York, NY, (1978).
3. T.E. Wheldon, *Mathematical Models in Cancer Research*, Adam Hilger, Bristol, England, (1988).
4. G.I. Bell, Predator-prey equations simulating an immune response, *Math. Biosci.* **16**, 291–314 (1973).
5. G.H. Pimbley, Periodic solutions of predator-prey equations simulating an immune response, I, *Math. Biosci.* **20**, 27–51 (1974).
6. G.H. Pimbley, Periodic solutions of predator-prey equations simulating an immune response, II, *Math. Biosci.* **21**, 251–277 (1974).
7. R. Lefever and R.P. Garay, Local description of immune tumor rejection, In *Biomathematics and Cell Kinetics*, (Edited by A.J. Valleron and P.D.M. MacDonald), Elsevier, Amsterdam, pp. 333–344, (1978).
8. I. Prigogine and R. Lefever, Stability problems in cancer growth and nucleation, *Comp. Biochem. Physiol.* **67B**, 389–393 (1980).
9. P.C. Fife, Mathematical aspects of reacting and diffusing systems, In *Lecture Notes in Biomathematics*, Vol. 28, Springer-Verlag, New York, NY, (1979).
10. R. Lefever and T. Erneux, On the growth of cellular tissues under constant and fluctuating environmental conditions, In *Nonlinear Electrodynamics in Biological Systems*, (Edited by W. Ross and A. Lawrence), Plenum Publishing Corporation, New York, NY, pp. 287–305, (1984).
11. R. Lefever and W. Horsthemke, Bistability in fluctuating environments. Implications in tumor immunology, *Bull. Math. Biol.* **41**, 469–490 (1979).
12. A.-S. Qi, Multiple solutions of model describing cancerous growth, *Bull. Math. Biol.* **50**, 1–17 (1988).
13. A.S. Goustin, E.B. Loef, G.D. Shipley and H.L. Moses, Growth factors and cancer, *Cancer Res.* **46**, 1015–1018 (1986).
14. M.B. Sporn and G.J. Todaro, Autocrine secretion and malignant transformation of cells, *New Engl. J. Med.* **303**, 878–880 (1980).
15. M.B. Sporn and A.B. Roberts, Autocrine growth factors and cancer, *Nature* **313**, 745–747 (1985).
16. A.B. Roberts, M.A. Anzano, L.M. Wakefield, N.S. Roche, D.F. Roche, D.F. Stern and M.B. Sporn, Type beta transforming growth factor: A bifunctional regulator of cellular growth, In *Proc. Nat. Acad-Sci.*, pp. 119–121, (1985).
17. J.L. Marx, How cancer cells spread in the body, *Science* **244**, 47–48 (1989).
18. J.A. Adam, Self-activation and inhibition, *App. Math. Lett.* **4**, 85–87 (1991).
19. J.A. Adam, Diffusion models of prevascular and vascular tumor growth—A review, In *Lecture Notes in Pure and Applied Mathematics*, Vol. 131, Ch. 41, pp. 625–642, Marcel Dekker, Inc., New York, NY, (1991).
20. J.D. Murray, *Mathematical Biology*, Springer-Verlag, New York, NY, (1989).
21. P.C. Fife and J.B. McLeod, The approach of solutions of nonlinear diffusion equations of travelling front solutions, *Archiv. Rat. Mech. Anal.* **65**, 335–361 (1977).
22. A. Nitzan, P. Ortoleva and J. Ross, Nucleation in systems with multiple stationary states, In *Symposium #9 of the Faraday Society*, Faraday Division Chemical Society, London, pp. 241–253, (1975).
23. L.D. Landau and E.M. Lifschitz, *Statistical Physics*, Addison-Wesley, Reading, MA, (1958).
24. E. Beltrami, *Mathematics for Dynamic Modeling*, Chapter 6, Academic Press, Orlando, FL, (1987).
25. J.A. Adam, A simplified mathematical model of tumor growth, *Math. Biosci.* **81**, 229–244 (1986).
26. D. G. Kendall, A form of wave propagation associated with the equation of heat conduction, *Proc. Camb. Phil. Soc.* **44**, 591–594 (1948).
27. R.P. Garay and R. Lefever, A kinetic approach to the immunology of cancer: Stationary state properties of effector-target cell reactions, *J. Theor. Biol.* **73**, 417–438 (1978).
28. G. Derise and J.A. Adam, A generalization of a solvable model in population dynamics, *J. Phys. A. Math. Gen.* **23**, L727S–L731S (1990).
29. S. Michelson and J. Leith, Autocrine and paracrine growth factors in tumor growth: A mathematical model, *Bull. Math. Biol.* **53**, 639–656 (1991).
30. D.G. Aronson and H.F. Weinberger, Nonlinear diffusion in population genetics, combustion and nerve pulse propagation, *Lecture Notes in Mathematics* **446**, 5–49 (1975).
31. R.A. Fisher, The wave of advance of advantageous genes, *Ann. Eugenics* **7**, 353–369 (1937).
32. A. Kolmogoroff, I. Petrovsky and N. Piscounoff, Etude de l'equation de la diffusion avec croissance de la quantité de matiere et son application à un probleme biologique, *Moscow Univ. Bull. Math.* **1**, 1–25 (1937).

APPENDIX 1

LOCAL STABILITY OF THE STEADY STATES

We have defined $m_i(x) = p'_i(x) - \frac{\beta x}{1+x}$ from equations (25) and (54). For each $i = 1, 2, 3, 4$, there is a steady state at $x = 0$, and at $x = x_s$, where $x_s > 0$ is a solution of $\beta = (1 + x^{-1})p'_i(x)$. We treat each case in turn.

$i = 1$

$$m'_1 = 1 - 2\theta_1 x - \beta(1+x)^{-2}.$$

Note that $m'_1(0) = 1 - \beta \leq 0$ according as $\beta \geq 1$. The null state is stable if $\beta > 1$. Using

$$\beta = (1+x_s)(1-\theta_1 x_s),$$

we find

$$(1+x_s)m'_1(x_s) = x_s(1-\theta_1-2\theta_1 x_s). \quad (\text{A1})$$

Hence, if $\theta_1 < 1$, $m'_1(x_s) \leq 0$ if $x_s \geq \frac{1-\theta_1}{2\theta_1}$; if $\theta_1 > 1$, $m'_1(x_s) < 0$ and the state is stable. Note that

$$\beta \left(\frac{1-\theta_1}{2\theta_1} \right) = \frac{(1+\theta_1)^2}{4\theta_1} = \beta_c \quad (\text{see Figure 3(a)}). \quad (\text{A2})$$

$i = 2$ (Activator)

$m'_2 = 1 - 3\theta_2^2 x^2 - \beta(1+x)^{-2}$. As for $i = 1$, $m'_2(0) = 1 - \beta$. Using $\beta = (1+x_s)(1-\theta_2^2 x_s^2)$, we find

$$(1+x_s)m'_2(x_s) = x_s(1-2\theta_2^2 x_s-3\theta_2^2 x_s^2). \quad (\text{A3})$$

From this, it follows that

$$m'_2(x_s) \begin{cases} < 0 \\ > 0 \end{cases} \quad \text{when} \quad x_s \begin{cases} > \\ < \end{cases} \left\{ \left(\frac{1+3}{\theta_2^2} \right)^{\frac{1}{2}} - 1 \right\} / 3 = \alpha_*.$$

After some algebra, we find

$$\beta(\alpha_*) = \frac{2}{27\theta_2} \{ (\theta_2^2 + 3)^{\frac{3}{2}} + 9\theta_2 - \theta_2^3 \} = \beta_c. \quad (\text{A4})$$

$i = 3$ (Inhibitor)

$$m'_3 = 1 - 4\theta_3 x + 3\theta_3^2 x^2 - \beta(1+x)^{-2}.$$

As for $i = 1$ and 2 , $m'_3(0) = 1 - \beta$. Using $\beta = (1+x_s)(1-\theta_3 x_s)^2$, we find

$$(1+x_s)m'_3(x_s) = x_s(3\theta_3^2 x_s^2 + 2\theta_3(\theta_3 - 2)x_s - 2\theta_3 + 1)$$

whence

$$m'_3(x_s) < 0 \quad \text{if} \quad \frac{1-2\theta_3}{3\theta_3} < x_s < \frac{1}{\theta_3} \quad (\text{A5})$$

and $m'_3(x_s) > 0$ if $x_s < \frac{1-2\theta_3}{3\theta_3}$ or $x_s > \frac{1}{\theta_3}$.

Note that if $\theta_3 > \frac{1}{2}$, there is only one unstable branch $x_s > 1/\theta_3$. Note also that

$$\beta \left(\frac{1-2\theta_3}{3\theta_3} \right) = \frac{4(1+\theta_3)^3}{27\theta_3} = \beta_c \quad (\text{A6})$$

and $\beta(1/\theta) = 0$.

$i = 4$ (Delayed Inhibitor)

$$m'_4 = 2\rho x - 3\rho\theta_4 x^2 - \beta(1+x)^{-2}.$$

Now $m'_4(0) = 0$, and $\beta = (1+x_s)x_s\rho(1-\theta_4 x_s)$, whence

$$(1+x_s)m'_4(x_s) = \rho x_s(1+2(1-\theta_4)x_s-3\theta_4 x_s^2), \quad (\text{A7})$$

so $m'_4(x_s) \leq 0$ for $x_s \geq \frac{1-\theta_4+\sqrt{(1-\theta_4)^2+3\theta_4}}{3\theta_4} = \alpha^*$.

We find

$$\beta(\alpha^*) = \rho\alpha^*(1+\alpha^*)(1-\theta_4\alpha^*). \quad (\text{A8})$$

APPENDIX 2

RIGOROUS RESULTS ON (10)

Aronson and Weinberger [30], guided by the context of genetics, divided the system

$$u_t = u_{xx} + f(u), \quad f \in C^1[0, 1], \quad f(0) = f(1) = 0,$$

into three cases. The case considered by Fisher [31] and Kolmogoroff *et al.* [32] in which

$$f'(0) > 0, \quad f(u) > 0 \text{ in } (0, 1),$$

they called the *heterozygote intermediate* case. The *heterozygote superior* case is defined by

$$f'(0) > 0, \quad f'(1) > 0, \quad f(u) > 0 \text{ in } (0, \alpha),$$

$$f(u) < 0, \text{ in } (\alpha, 1), \text{ for some } \alpha \in (0, 1),$$

and the *heterozygote inferior* case is defined by

$$f'(0) < 0, \quad f'(1) < 0, \quad f(u) > 0 \text{ in } (\alpha, 1)$$

for some $\alpha \in (0, 1)$, $f(u) < 0$ in $(0, \alpha)$ for some $\alpha \in (0, 1)$, and $\int_0^1 f(u) du > 0$.

For the most part in this paper, we are concerned with the heterozygote intermediate and inferior cases, or modifications of them. In the former case, Kolmogoroff *et al.* [32] proved the existence of a number c_{\min} such that the system possesses traveling wave solutions $u(x, t) = \xi(x - ct)$ for all velocities c , $|c| \geq c_{\min}$. In addition, they proved that the initial data

$$u(x, 0) = \begin{cases} 1, & x < 0, \\ 0, & x > 0, \end{cases}$$

converges (in a certain sense) to a travelling wave solution with speed c_{\min} . Aronson and Weinberger [30] study the stability properties of the equilibrium states $u \equiv 0, \alpha$ and 1 for the initial value problem, noting that in the heterozygote inferior case, threshold phenomena can be expected, i.e., a disturbance of bounded support of the state $u \equiv 0$ which is sufficiently large on a sufficiently large interval grows to one, while a disturbance which is not sufficiently large in these two senses dies out.

Fife and McLeod [21] discuss the heterozygote inferior case for initial data without compact support and show that under some circumstances, u approaches a pair of diverging wavefronts. They also consider cases where f has more than one internal zero. The monograph by Fife [9] has many interesting details to which the unfamiliar reader is referred.

Stability of the travelling waves has been of particular interest (see the summary in Chapter 11 of [20]) in the sense of how various initial data evolve and to what limiting asymptotic functional form they tend.

APPENDIX 3

TRAVELLING WAVEFRONT SOLUTIONS FOR FISHER'S EQUATION

The term $m_i(x)$ in equation (10) is $x(1-x)$ in Fisher's equation. From the phase plane analysis in Section 4, it follows that the eigenvalues corresponding the point $(0, 0)$ are

$$\lambda_{1,2} = \frac{1}{2} \left\{ -c \pm (c^2 - 4)^{\frac{1}{2}} \right\}, \quad (\text{A3.1})$$

while those for $(1, 0)$ are

$$\lambda_{1,2} = \frac{1}{2} \left\{ -c \pm (c^2 + 4)^{\frac{1}{2}} \right\}. \quad (\text{A3.2})$$

Clearly, if $c^2 \geq c_{\min} = 2$ the origin is a stable node, and $(1, 0)$ is a saddle point whatever the value of c . The eigenvectors are $(1, \lambda_i)^t$, $i = 1, 2$, and by considering an appropriate region of the $\phi - \phi'$ plane (see [21]), Ω , such that a branch of the unstable manifold of the saddle point joins up with the stable node, the existence of a $\phi(\xi)$, $\{\phi'(\xi) < 0, \phi(-\infty) = 1, \phi(\infty) = 0\}$ is established. For each segment of the boundary, the phase flow is inward across the boundary. The region Ω is thus an invariant of the flow (all orbits originating with Ω remain there). Furthermore, any limit cycles would have to contain an equilibrium point, but $(0, 0)$ and $(1, 0)$ are on the boundary, so no limit cycles exist. The point $(1, 0)$ is repelling within Ω , so its unstable manifold must tend to the attractor at the origin. There is no other dynamic behavior possible, by the Poincare-Bendixson theorem.